REMARKS

Claims 1-12 and 14-24 are currently pending in this application. No new matter has added.

Rejections under 35 U.S.C. 103

The Examiner has rejected claims 1, 2, 8 and 14-24 under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,506,222 ("Stefano") in view of Schafer-Korting, *et al.*, "Delivery of Lipophilic Compounds with Lipid Nanoparticles-Applications in Dermatics and for Transdermal Therapy," *Lipospheres in Drug Targets and Delievery*, CRC Press (2005) ("Schafer-Korting"), in further view of http://redpoll.pharmacy,ualberta.ca/drugbank ("DrugBank") and of references cited in Schafer-Korting, specifically, reference 9, Mehnert and Mader, "Solid lipid nanoparticles: Production, characterization and applications," *Adv. Drug Deliv. Rev.* 47:165-196 (2001) and Reference 29, zur Muhlen, *et al.*, "Solid Lipid Nanoparticles for Controlled Drug Delivery," *Eur. J. Pharm. Biopharm.* 45:149-155 (1998). Applicants traverse.

Regarding claims 1 and 2, the Examiner submits that Schafer-Korting teaches solid lipid nanoparticles (50 to 1000 nm) for topical application having a drug enriched core with a lipid crystal shell, formed as a function of the lipid's melting point and the relative solubilities of the drug and the lipid and therefore the drug enriched core is formed when the drug precipitates before the lipid crystallizes. (*See*, Office Action at page 4). Further, the Examiner indicates that because enhanced skin permeation occasioned by the use of the nanoparticulate dosage form obviates the need for additional formulation components (*e.g.* Stefano's permeation enhancers), it would have been obvious to a skilled artisan to have combined the formulation taught by Stefano with the liquid crystalline nanoparticulate lipid taught by Schafer-Korting to obtain a topical dosage form of spironolactone with bioavailability resulting from the use of nanoparticlates rather than formulated permeation enhancers. (*See*, Office Action at pages 5-6).

Regarding claims 8, 14-19, 23 and 24, the Examiner indicates it would have been obvious to a skilled artisan to combine the topical spironolactone formulation and dosing information of Stefano with the skin permeation enhancing nanocrystallinity of Schafer-

Korting to treat the effects of increased androgenic activity with a topical treatment. (*See*, Office Action at page 5). Further, regarding claim 20, the Examiner indicates it would have been obvious to combine the skin permeation enhancing oriented crystalline network system taught by Schafer-Korting with the incorporated substance for use in topical treatment of acne as taught by Stefano. (*See*, Office Action at page 5). Additionally, regarding claims 21 and 22, the Examiner submits that while Schafer-Korting do not teach specific particles in the size range of from 300 nm to 900 nm, it teaches that drug penetration into the skin strata is strongly related to particle size with "particles smaller than 400 nm [proving] to be most potent." (*See*, Office Action at page 6). The Examiner then indicates that adjustment of particular working conditions, *i.e.* particle size, is merely a matter of judicious selection and routine optimization. (*See*, Office Action at page 6).

Applicants submit that Schafer-Korting is not available as prior art under 103(a). Specifically, the instant application is a national stage entry of PCT/GB2002/005680, which was filed on December 13, 2002 and Schafer-Korting was published in 2005 and cannot be asserted against the claimed invention. As such, Applicants submit that this rejection has been overcome.

Applicants respectfully request that rejection be withdrawn.

The Examiner has also rejected claims 3-5 under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Schafer-Korting and in further view of http://ches.us.edu/departments/nhm/faculty/lane/nhm454/McWCh11&12fats.pdf ("Lane"). Applicants traverse.

The Examiner indicates that the teachings of Schafer-Korting and Stefano are as described above, but that both are silent regarding lipid crystallization temperature, but that Lane teaches lipids with a crystallization temperature in the range of 70°C and also teaches β-crystal of the monoglycerides of C_{18} fatty acids. (*See*, Office Action at page 6). Further, the Examiner submits that it is within the prevue of the skilled artisan to adjust the crystallization temperature by judicious selection of formulation components such as those utilized in the pending claims. (*See*, Office Action at page 6).

Again, Applicants submit that Schafer-Korting is not available as prior art under 103(a). Specifically, the instant application is a national stage entry of PCT/GB2002/005680,

which was filed on December 13, 2002 and Schafer-Korting was published in 2005 and cannot be asserted against the claimed invention. Similarly, Lane has a publication date of 2004 and therefore cannot be properly asserted against the claimed invention as well. As such, Applicants submit that this rejection has been overcome.

Applicants respectfully request that rejection be withdrawn.

The Examiner has also rejected claims 6, 7 and 9-12 under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Schafer-Korting and in further view of US Patent No. 6,228,383 ("Hansen") and Kirk-Othmer Encyclopedia of Chemical Technology (2001), Wiley Interscience ("Kirk-Othmer"). Applicants traverse.

The Examiner submits that the teachings of Schafer-Korting and Stefano are as discussed above, but fail to disclosure the solvent in which the nanoparticulate is formed, however, the Examiner believes that Hansen teaches that the lipid crystals are formed from polar liquids such as water and glycerol, and that the lipid crystals are comprised of glyceryl monoesters of C_{18} fatty acids. (*See*, Office Action at page 7). Regarding claims 9-12, the Examiner submits that the teachings of Hansen and Schafer-Korting are as discussed above with Hansen further teaching that the composition may be characterized as a suspension and that is further comprises a stabilizer, which would have been an obvious addition to the formulation in order to maintain the suspension over the time and temperature ranges required to yield a useful product. (*See*, Office Action at page 7). Additionally, the Examiner indicates that while Schafer-Korting and Hansen fail to disclose sodium docusate specifically as a stabilizer, but that Hansen teaches solubilizing agents generally and that Kirk-Othmer teaches sodium docusate is a surface active agent, *i.e.* solubilizing agent. (*See*, Office Action at page 7-8).

As discussed above, Applicants submit that Schafer-Korting is not available as prior art under 103(a). Specifically, the instant application is a national stage entry of PCT/GB2002/005680, which was filed on December 13, 2002 and Schafer-Korting was published in 2005 and cannot be asserted against the claimed invention. As such, Applicants submit that this rejection has been overcome.

Applicants respectfully request that rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance. An action progressing this application to issue is courteously urged. If the Examiner is of the opinion that further discussion of the application would be helpful, the Examiner is respectfully requested to telephone the Applicant's undersigned.

Respectfully submitted,

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Date: August 6, 2008